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PH#12

February 26, 2001

Commissioner for Patents
Washington, D.C. 20231

Re: U.S. Utility Patent Application
Appl. No. 09/402,713; § 371 Date: June 13, 2000
For: **PCA3, PCA3 Genes, and Methods of Use**
Inventor: Marion J.G. Bussemakers
Our Ref: 1619.0020001/SRL/TBB

Sir:

Transmitted herewith for appropriate action are the following documents:

1. First Supplemental Information Disclosure Statement, with Exhibits 1-11; and

2. Return postcard.

It is respectfully requested that the attached postcard be stamped with the date of filing of these documents, and that it be returned to our courier. In the event that extensions of time are necessary to prevent abandonment of this patent application, then such extensions of time are hereby petitioned.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036. A duplicate copy of this letter is enclosed.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Jorge A. Goldstein
Attorney for Applicant
Registration No. 29,021

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Enclosures

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	
Bussemakers, Marion J.G.	Art Unit: 1643
Appl. No.: 09/402,713	Examiner: Tedeschi, B.
§ 371 Date: June 13, 2000	Atty Docket: 1619.0020001
For: **PCA3, PCA3 Genes, and Methods of Use**	

IDS submitted by the examiner 4-29-03, mg

First Supplemental Information Disclosure Statement

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

Under the duty to disclose information that may be material to the prosecution of the above-noted application, Applicant hereby submits a recount of correspondence and information that may or may not be relevant to the determination of inventorship of the claimed invention as disclosed in the current application.

Applicant reserves the right to establish that she is the sole inventor of the claimed invention over any of the information provided herewith, and/or to prove that this information may be used to establish that no other person should be listed as inventor of the claimed invention as disclosed in the current application.

This statement should not be construed as a representation that Applicant believes that a valid dispute of inventorship exists, nor that the information as disclosed herein is proof that additional inventors should be included on the current application.

Events Leading to Filing of Provisional Application 60/025,224

At the beginning of 1993, Dr. Marion Bussemakers, the named inventor, was employed as a postdoctoral fellow in Dr. William Isaacs' lab at Johns Hopkins University (JHU) and given a "free hand" to create and develop any project of her choosing. While serving in this role as postdoctoral fellow, Dr. Bussemakers decided to use a technique called differential display to search for mRNAs that may be overexpressed or underexpressed during prostatic tumor progression. Dr. Bussemakers conceived of the project on her own, and while Dr. Isaacs was present to follow the progress of Dr. Bussemakers' project and to give advice when needed, Dr. Bussemakers essentially worked autonomously within Dr. Isaacs' laboratory. It was during this time period as a postdoctoral fellow that Dr. Bussemakers discovered a DNA fragment that appeared to be overexpressed in human prostate tumors, and named the DNA fragment DD3. This discovery of the DD3 fragment was the result of work that Dr. Bussemakers conceptualized and performed solely on her own while in Dr. Isaacs' lab. During her employment at JHU, Dr. Bussemakers identified a total of 3 cDNA transcripts that were overexpressed in prostatic tumors and named the fragments DD3, DD3.1 and DD3.2, with DD3 being subsequently used to identify two major mRNA transcripts. Although the initial isolation of the DD3 clones was performed in Dr. Isaacs' lab at JHU, none of the DD3 clones was sequenced at JHU or under the auspices of Dr. Isaacs, and none of the DD3 clones isolated in Dr. Isaacs' lab was specifically an open reading frame (ORF) for a particular gene.

The Filing of Provisional Application 60/025,224

Based on Dr. Bussemakers' work in Dr. Isaacs' lab, a provisional application (serial number 60/025,224) ("the '224 application") was filed in the U.S. Patent and Trademark office, listing Marion Bussemakers and William Isaacs as inventors on September 19, 1996. Additionally, the '224 application contains a statement asserting that the U.S. Government may have certain rights to the invention as disclosed in the application. The '224 application disclosed the sequence of the DD3 fragment that was believed to be overexpressed in human prostatic tumors. At the time of filing, the '224 patent did not mention a complete gene or an ORF, and only discussed the potential use of DD3 as a selective probe for diagnostic purposes.

The undersigned believes that the '224 application has not been converted to a non-provisional application and thus has been abandoned, based on correspondence to the undersigned from JHU. (*See* Exhibit 1).

Events Leading to the Filing of Provisional Application 60/041,836

After returning to The University of Nijmegen in The Netherlands, Dr. Bussemakers, with the consent of Dr. Isaacs, began to analyze the DD3 clones she had obtained as a postdoc while at JHU. After approximately two and a half years of sequencing and analysis of the DD3 clone, performed entirely at The University of Nijmegen, Dr. Bussemakers discovered that a complete ORF existed within DD3. Briefly, to define the complete gene that was encoding DD3, Dr. Bussemakers constructed a cDNA library and used DD3 as a probe to identify over 250 positive clones, 80 of which were analyzed further. From the 80 clones, Dr. Bussemakers

discovered that at least 4 different transcripts arise from DD3 due to alternative splicing. Analysis of these 4 splice variants revealed the complete ORF for the protein encoding region. This complete ORF was later named PCA3.

The level of conception required, and the techniques used to identify the ORF within the DD3 fragment (PCA3) were conceptualized, initiated and carried out solely under the direction of Dr. Bussemakers while at The University of Nijmegen.

Prosecution History of the Current Application (U.S. Serial Number 09/402,713) in Brief

Based on her work performed entirely at The University of Nijmegen in elucidating the ORF of DD3 (PCA3), a provisional application (serial number 60/041,836) ("the '836 application") was filed at the U.S. Patent and Trademark Office, listing Marion J.G. Bussemakers as the sole inventor, on April 10, 1997. The '836 application relates to the PCA3 gene, which is specifically the ORF of a gene that is overexpressed in prostate cancer. The '836 application also relates to methods of using PCA3 in producing proteins, antibodies and transcripts, all of which may be used in diagnosing or treating prostate cancer.

On April 9, 1998, International Application number PCT/CA98/00346 ("the PCT application") was filed, claiming benefit of the '836 application. The PCT application was subsequently published on October 15, 1998.

On October 8, 1999, U.S. National Phase of the PCT application was filed at the U.S. Patent and Trademark Office, listing Marion J.G. Bussemakers as the sole inventor.

On July 5, 2000, the U.S. Patent and Trademark Office mailed a Notice of Acceptance Under 35 U.S.C. § 371 for the PCT application and established June 13, 2000 as the 35 U.S.C.

§ 102(e) date. The application was assigned serial number 09/402,713 ('the '713 application"). To date, the Examiner has not issued an Office Action on the merits of the '713 application.

Possible Dispute of Inventorship

Dr. Bussemakers discovered the DD3 fragment while employed at the laboratory of Dr. Isaacs at JHU, and the prior '224 application was filed because of this effort. Indeed, the '224 application, relating to DD3 and making no mention of a complete ORF, lists Drs. Marion Bussemakers and William Isaacs as co-inventors. However, the '224 application relates only to the DD3 fragment and a discussion that the fragment may be used for diagnostic purposes.

In contrast, the present '713 application relates to the complete PCA3 gene and its methods of use in diagnosing and treating prostate cancer. Dr. Marion Bussemakers, who discovered PCA3 and conceived of the methodology used to define PCA3, is listed as the sole inventor of the '713 application.

It is the position of JHU that Dr. Isaacs should also be listed as a co-inventor on the '713 application, which relates strictly to PCA3 and its uses. JHU feels that isolation of the DD3 fragment directly lead to the discovery of the PCA3 ORF, and because some of the work in isolating DD3 was performed at Dr. Isaacs' lab, Dr. Isaacs may be a co-inventor of the current application. In support of this position, JHU submits that while Dr. Bussemakers was isolating DD3, Dr. Isaacs provided the full resources of his laboratory and provided guidance when "impediments occurred," in the isolation of DD3. JHU also asserts that Dr. Bussemakers could not have discovered the ORF of the PCA3 gene without relying on the work that was performed in Dr. Isaacs' lab. (*See* Exhibit 2).

However, the level of conception and the experimentation performed in defining PCA3 from the DD3 sequence was a non-obvious process, towards which Dr. Isaacs made no contributions. Dr. Bussemakers conceived of the cloning and sequencing strategy, and analyzed the data including splice variants, solely on her own while at The University of Nijmegen. Furthermore, the availability of the DD3 clone was in the public domain as a result of abstract publications of presentations at scientific meetings, prior to Dr. Bussemakers' attempts to define the ORF. (*See* Exhibits 3-9). Thus any conceptual contribution that Dr. Isaacs may have contributed to the complete, well-defined ORF was in the public domain prior to Dr. Bussemakers' efforts to define the ORF.

Dr. Isaacs in fact believed that the DD3 clone was an invention capable of standing on its own and that obtaining the complete ORF would be a worthwhile pursuit, albeit one for the future. For example, after meeting Dr. Bussemakers at a meeting in Chapel Hill in 1995, Dr. Isaacs sent an e-mail to her on December 13, 1995 in which he stated that: "Regarding DD3, your data does indeed look interesting as you showed me and on your poster. *Although an open reading frame would be nice*, the tissue specificity of expression is sufficient to warrant further study. . . ." (Emphasis added). (*See* Exhibit 10). Also, in the Report of Invention signed by Dr. Isaacs on October 21, 1996, he states that ". . . DD3 is the most prostate-cancer-specific transcript described to date. As such, DD3 is a promising new marker for prostate cancer *with important potential diagnostic value*. . . ." (Emphasis added) (*See* Exhibit 11).

It is also the position of JHU that because the work done on DD3 at Dr. Isaacs' lab utilized federal grant money, the U.S. Government may have certain rights to the invention involving the PCA3 gene and its uses. However, as in the above analysis, the non-obvious and independent process of discovering and defining the ORF within DD3 was conceived and

performed solely by Dr. Bussemakers while she was at The University of Nijmegen. No Federal funds of the United States were used therefor. Additionally, the product of the work that was performed with the aide of Federal grant money was published prior to Dr. Bussemakers' attempts to define the ORF.

Conclusion

Applicant submits this Information Disclosure Statement under 37 C.F.R. § 1.56. The Examiner may find that information disclosed herein may be material to the prosecution of the above-captioned application.

It is undisputed that Dr. Bussemakers was employed in the laboratory of Dr. Isaacs when Dr. Bussemakers discovered DD3. Furthermore, the efforts of Dr. Bussemakers while at JHU resulted in the discovery of DD3, which was the subject matter of provisional application 60/025,224, filed September 19, 1996. Additionally, data regarding DD3, such as nucleotide sequence analysis that was produced by Dr. Bussemakers in Dr. Isaacs' lab, was placed in the public domain via presentations and abstracts of scientific meetings. (*See* Exhibits 3-9).

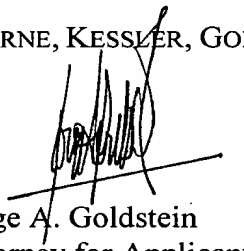
However, the independent, subsequent and non-obvious process of discovering and defining the ORF that was later named PCA3 was conceived and performed entirely under the direction of Dr. Bussemakers while at The University of Nijmegen. Dr. Isaacs made no contributions towards the discovery or reduction to practice of PCA3. Because Dr. Bussemakers conceived of PCA3 and reduced it to practice while at The University of Nijmegen, in The Netherlands, Dr. Bussemakers should be listed as the sole inventor of the current application with no rights assigned to the U.S. Government.

This Information Disclosure Statement is being filed within three months of the U.S. filing date or before the mailing date of a first Office Action on the merits. No certification or fee is required.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036. A duplicate copy of this pleading is enclosed.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



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